REMARKS

STATUS OF THE CLAIMS

Claims 1-67 are pending. Applicants' representative acknowledges that the Examiner has found the pending claims to be free of the prior art (see §5, line 1 in the February 22, 2002 Office Action, Paper No. 10). For the Examiner's convenience, Applicants' representative has attached the pending claims as an appendix.

This response refers to the paragraph numbering in the Office Action (Paper Number 10) in responding to the Examiner's remarks.

PRELIMINARY ADMINISTRATIVE MATTERS

Drawings

The Examiner objected to the drawings. Applicants' representative has revised the drawings in response to the Examiner's concerns. Copies of the revised drawings are attached as an appendix.

Oath/Declaration

3. The Examiner contends that the oath or declaration is defective because the oath or declaration does not claim priority to the parent application U.S.S.N. 09/083,793 as stated in the specification. Applicants do not believe the oath or declaration to be defective (*see* Rule 1.63). However, to expedite prosecution, Applicants submit herewith as a separate paper a revised Oath/Declaration establishing priority to the parent application as requested by the Examiner.

Claims 1-67 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Murphy *et al.* (WO 98/53078). The Examiner states that this rejection will be maintained until a new declaration is filed. In view of the revised declaration discussed above, Applicants respectfully request that the rejection of claims 1-67 under 35 U.S.C. §103(a) as allegedly unpatentable over Murphy *et al.* (WO 98/53078) be withdrawn.

DOUBLE PATENTING REJECTIONS

4a. Claims 1-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 91, 96-117, 122-129 and 141-143 of copending application U.S.S.N. 09/083,793. Although the conflicting claims are not identical, the Examiner asserts that these claims are not patentably distinct from each other because the human-bovine chimeric claimed in the instant claims is disclosed in claims 91, 96-117, 122-129 and 141-143 of copending application U.S.S.N. 09/083,793.

Applicants note that this is a provisional obviousness-type double patenting rejection. Accordingly, Applicants will take appropriate action to obviate the rejection upon indication by the Office of allowable, conflicting subject matter in one of the subject applications.

4b. Claims 1-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 91-93, 97-100 and 102-128 of copending application U.S.S.N. 09/424/628. Although the conflicting claims, are not identical, the Office contends that they are not patentably distinct because the chimeric human-bovine claimed in the instant claims is allegedly disclosed in claims 91-93, 97-100 and 102-128 of copending application U.S.S.N. 09/424/628.

Applicants note that this is a provisional obviousness-type double patenting rejection. Accordingly, Applicants will take appropriate action to obviate the rejection upon indication by the Office of allowable, conflicting subject matter in one of the subject applications.

4c. Claims 1-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-4, 42, 44-50, 55-61, 74, 77-79 and 81-94 of copending application U.S.S.N. 09/733,692. Although the conflicting claims are not identical, the Office contends that they are not patentably distinct from each other because the chimeric human bovine claimed in the instant claims is allegedly disclosed in claims 1-4, 42, 44-50, 55-61, 74, 77-79 and 81-94 of copending application U.S.S.N. 09/733,692.

Applicants note that this is a provisional obviousness-type double patenting rejection. Accordingly, Applicants will take appropriate action to obviate the rejection upon indication by the Office of allowable, conflicting subject matter in one of the subject applications.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Date: 8/22/02

Respectfully submitted,

Jeffrey J. King
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Enclosure: Executed Oath and Declaration

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PENDING CLAIMS

1. An isolated infectious human-bovine chimeric parainfluenza virus (PIV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase protein (L), and a partial or complete PIV background genome orantigenome of a human PIV (HPIV) or bovine PIV (BPIV) combined with one or more heterologous gene(s) or genome segment(s) of a different PIV to form a human-bovine chimeric PIV genome or antigenome.

2. The chimeric PIV of claim 1, wherein said one or more heterologous gene(s) or genome segment(s) encodes one or more PIV N, P, C, D, V, M, F, HN and/or L protein(s) or fragment(s) thereof.

3. The chimeric PIV of claim 1, wherein said one or more heterologous gene(s) or genome segment(s) encodes a complete open reading frame (ORF) of one or more PIV N, P, C, D, V, M, F, HN and/or L protein(s).

4. The chimeric PIV of claim 1, wherein said one or more heterologous gene(s) or genome segment(s) includes a heterologous regulatory element comprising an extragenic 3' leader or 5' trailer region, a gene-start signal, gene-end signal, RNA editing site, encapsidation signal, intergenic region, or 3' or 5' non-coding region.

5. The chimeric PIV of claim 1, wherein said background genome or antigenome incorporates a heterologous genome segment integrated with the background genome or antigenome to form a chimeric gene.

6. The chimeric PIV of claim 5, wherein said chimeric genome or antigenome encodes a chimeric glycoprotein.

7. The chimeric PIV of claim 1, wherein a heterologous gene or genome segment is substituted for a counterpart gene or genome segment in a partial PIV background genome or antigenome.

8. The chimeric PIV of claim 1, wherein a heterologous gene or genome segment is added adjacent to or within a noncoding region of the partial or complete PIV background genome or antigenome.

9. The chimeric PIV of claim 1, wherein a heterologous gene or genome segment is added or substituted at a position corresponding to a wild-type gene order position of a counterpart gene or genome segment within the partial or complete PIV background genome or antigenome.

10. The chimeric PIV of claim 1, wherein a heterologous gene or genome segment is added or substituted at a position that is more promoter-proximal or promoter-distal compared to a wild-type gene order position of a counterpart gene or genome segment within the partial or complete PIV background genome or antigenome.

11. The chimeric PIV of claim 1, wherein the chimeric genome or antigenome comprises a partial or complete BPIV background genome or antigenome combined with one or more heterologous gene(s) or genome segment(s) from a human
PIV.

12. The chimeric PIV of claim 11, wherein one or more HPIV glycoprotein genes selected from HN and F, or one or more genome segments encoding a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof, is/are substituted for one or more counterpart genes or genome segments within the BPIV background genome or antigenome.

13. The chimeric PIV of claim 11, wherein one or more HPIV glycoprotein genes selected from HN and F is/are substituted to replace one or more counterpart glycoprotein genes in the BPIV background genome or antigenome.

14. The chimeric PIV of claim 13, wherein both HPIV glycoprotein genes HN andF are substituted to replace counterpart HN and F glycoprotein genes in the BPIV background genome or antigenome.

15. The chimeric PIV of claim 13, which is rBPIV3-FHHNH.

16. The chimeric PIV of claim 11, wherein the human-bovine chimeric PIV genome or antigenome encodes a chimeric glycoprotein having a HPIV glycoprotein ectodomain, antigenic determinant or immunogenic epitope.

17. The chimeric PIV of claim 16, wherein the heterologous genome segment encodes a glycoprotein ectodomain.

18. The chimeric PIV of claim 11, wherein one or more HPIV glycoprotein genes HN and F, or a genome segment encoding a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof is added to or incorporated within a BPIV background genome or antigenome.

19. The chimeric PIV of claim 11, wherein the chimeric genome or antigenome is further modified by addition or substitution of one or more additional heterologous gene(s) or genome segment(s) from a human PIV within the partial or complete bovine background genome or antigenome to increase genetic stability or alter attenuation, reactogenicity or growth in culture of the chimeric virus.

20. The chimeric PIV of claim 1, wherein the chimeric genome or antigenome comprises a partial or complete human PIV background genome or antigenome combined with one or more heterologous genes or genome segments from a bovine PIV.

21. The chimeric PIV of claim 20, wherein the heterologous gene or genome segment encodes a bovine PIV3 N protein.

22. The chimeric PIV of claim 20, wherein a bovine PIV3 N open reading frame (ORF) is substituted for a human PIV3 N ORF in the chimeric genome or antigenome.

23. The chimeric PIV of claim 22, which is rHPIV3-NB.

24. The chimeric PIV of claim 1, wherein the genome or antigenome is further modified by introduction of one or more attenuating mutations identified in a biologically derived mutant PIV or other mutant nonsegmented negative stranded RNA virus.

25. The chimeric PIV of claim 24, wherein the genome or antigenome incorporates at least one and up to a full complement of attenuating mutations present within PIV3 JS cp45.

26. The chimeric PIV of claim 24, wherein the genome or antigenome incorporates at least one and up to a full complement of attenuating mutations specifying an amino acid substitution in the L protein at a position corresponding to Tyr942, Leu992> or Thrlssa of JS; in the N protein at a position corresponding to residues Va196 or Ser389 of JS, in the C protein at a position corresponding to Ile96 of JS, in the M protein at a position corresponding to Prol99 of JS in the F protein at a position corresponding to residues Ile42o or Ala45o of JS, in the HN protein at a position corresponding to residue Va1384 of JS, a nucleotide substitution a 3' leader sequence of the chimeric virus at a position corresponding to nucleotide 23, 24, 28, or 45 of JS cp45, and/or a mutation in an N gene start sequence at a position corresponding to nucleotide 62 of JS cp45.

27. The chimeric PIV of claim 24, wherein the genome or antigenome incorporates attenuating mutations from different biologically derived mutant PIVs.

28. The chimeric PIV of claim 24, wherein the genome or antigenome incorporates an attenuating mutation at an amino acid position corresponding to an amino acid position of an attenuating mutation identified in a heterologous, mutant negative stranded RNA virus.

29. The chimeric PIV of claim 24, wherein the genome or antigenome includes at least one attenuating mutation stabilized by multiple nucleotide changes in a codon specifying the mutation.

30. The chimeric PIV of claim 1, wherein the genome or antigenome comprises an additional nucleotide modification specifying a phenotypic change selected from a change in growth characteristics, attenuation, temperature-sensitivity, cold adaptation, plaque size, host-range restriction, or a change in immunogenicity.

31. The chimeric PIV of claim 30, wherein the additional nucleotide

modification alters one or more of the PIV N, P, C, D, V, M, F, FIN and/or L genes and/or a 3' leader, 5' trailer RNA editing site, encapsidation signal, and/or an intergenic region.

32. The chimeric PIV of claim 30, wherein one or more genes of the chimeric virus is deleted in whole or in part or expression of the genes is reduced or ablated by a mutation in an RNA editing site, by a frameshift mutation, by a mutation that alters an amino acid specified by an initiation codon, or by introduction of one or more stop codons in an open reading frame (ORF) of the gene.

33. The chimeric PIV of claim 30, wherein a modification is introduced in the chimeric genome or antigenome comprising a partial or complete deletion of one or more C, D and/or V ORF(s) or one or more nucleotide change(s) that reduces or ablates expression of said one or more C, D and/or V ORF(s).

34. The chimeric PIV of claim 30, wherein the chimeric genome or antigenome is modified to encode a non-PIV molecule selected from a cytokine, a T lymphocyte helper epitope, a restriction site marker, or a protein of a microbial pathogen capable of eliciting a protective immune response in a mammalian host.

35. The chimeric PIV of claim 1, wherein the bovine-human chimeric genome or antigenome comprises a partial or complete PIV vector genome or antigenome combined with one or more heterologous genes or genome segments encoding one or more antigenic determinants of one or more heterologous pathogens.

36. The chimeric PIV of claim 35, wherein said one or more heterologous pathogens is a heterologous PIV and said heterologous gene(s) or genome segment(s) encode(s) one or more PIV N, P, C, D, V, M, F, HN and/or L protein(s) or fragment(s) thereof.

37. The chimeric PIV of claim 35, wherein the vector genome or antigenome is a partial or complete HPIV genome or antigenome and the heterologous gene(s) or genome segment(s) encoding the antigenic determinant(s) is/are of one or more heterologous PIV(s).

38. The chimeric PIV of claim 37, wherein said one or more heterologous PIV(s) is/are selected from HPIVI, HPIV2, or HPIV3.

39. The chimeric PIV of claim 37, wherein the vector genome or antigenome is a partial or complete HPIV genome or antigenome and the heterologous gene(s) or genome segment(s) encoding the antigenic determinant(s) is/are of one or more heterologous HPIV(s).

40. The chimeric PIV of claim 39, wherein the vector genome or antigenome is a partial or complete HPIV3 genome or antigenome and the heterologous gene(s) or genome segment(s) encoding the antigenic determinant(s) is/are of one or more heterologous HPIV(s).

41. The chimeric PIV of claim 40, wherein the chimeric genome or antigenome incorporates one or more gene(s) or genome segment(s) of a BPIV that specifies attenuation.

42. The chimeric PIV of claim 35, wherein one or more HPIV 1 or HPIV2 gene(s) or genome segment(s) encoding one or more HN and/or F glycoprotein(s) or antigenic domain(s), fragment(s) or epitope(s) thereof is/are added to or incorporated within the partial or complete HPIV3 vector genome or antigenome.

43. The chimeric PIV of claim 35, wherein both HPIV 1 genes encoding HN and F glycoproteins are substituted for counterpart HPIV3 HN and F genes to form a chimeric HPIV3-1 vector genome or antigenome which is further modified by addition or incorporation of one or more gene(s) or gene segment(s) encoding one or more antigenic determinant(s) of HPIV2 and one or more heterologous gene(s) or genome segment(s) of a BPIV that specifies attenuation.

44. The chimeric PIV of claim 43, wherein a transcription unit comprising an open reading frame (ORF) of an HPIV2 HN or F gene is added to or incorporated within the chimeric HPIV3-1 vector genome or antigenome.

45. The chimeric PIV of claim 35, wherein the vector genome or antigenome is a partial or complete BPIV genome or antigenome and the heterologous gene(s) or genome segment(s) encoding the antigenic determinant(s) is/are of one or more HPIV(s).

46. The chimeric PIV of claim 45, wherein said one or more antigenic determinant(s) is/are selected from HPIV 1, HPIV2 or HPIV3 HN and F glycoproteins and antigenic domains, fragments and epitopes thereof.

47. The chimeric PIV of claim 45, wherein one or more gene(s) or genome segment(s) encoding one or more antigenic determinant(s) of HPIV2 is/are added to or substituted within the partial or complete BPIV vector genome or antigenome.

48. The chimeric PIV of claim 45, wherein a plurality of heterologous genes or genome segments encoding antigenic determinants of multiple HPIVs are added to or incorporated within the partial or complete BPIV vector genome or antigenome.

49. The chimeric PIV of claim 35, wherein the vector genome or antigenome is a partial or complete HPIV genome or antigenome and the heterologous pathogen is selected from measles virus, subgroup A and subgroup B respiratory syncytial viruses, mumps virus, human papilloma viruses, type 1 and type 2 human immunodeficiency viruses, herpes simplex viruses, cytomegalovirus, rabies virus, Epstein Barr virus, filoviruses, bunyaviruses, flaviviruses, alphaviruses and influenza viruses.

50. The chimeric PIV of claim 35, wherein the vector genome or antigenome is a partial or complete BPIV genome or antigenome and the heterologous pathogen is selected from measles virus, subgroup A and subgroup B respiratory syncytial viruses, mumps virus, human papilloma viruses, type 1 and type 2 human immunodeficiency viruses, herpes simplex viruses, cytomegalovirus, rabies virus, Epstein Barr virus, filoviruses, bunyaviruses, flaviviruses, alphaviruses andinfluenza viruses.

51. The chimeric PIV of claim 50, wherein said one or more heterologous antigenic determinant(s) is/are selected from measles virus HA and F proteins, subgroup A or subgroup B respiratory syncytial virus F, G, SH and M2 proteins, mumps virus HN and F proteins, human papilloma virus L1 protein, type 1 or type 2 human immunodeficiency virus gp160 protein, herpes simplex virus and cytomegalovirus gB, gC, gD, gE, gG, gH, gI, gJ, gK, gL, and gM proteins, rabies virus G protein, Epstein Barr Virus gp350 protein; filovirus G protein, bunyavirus G protein, Flavivirus E and NS 1 proteins, and alphavirus E protein, and antigenic domains, fragments and epitopes thereof.

52. The chimeric PIV of claim 51, wherein the heterologous pathogen is measles virus and the heterologous antigenic determinant(s) is/are selected from the measles virus HA and F proteins and antigenic domains, fragments and epitopes thereof.

53. The chimeric PIV of claim 52, wherein a transcription unit comprising an open reading frame (ORF) of a measles virus HA gene is added to or incorporated within a HPIV3 vector genome or antigenome.

54. The chimeric PIV of claim 51, which incorporates a gene or genome segment from respiratory syncytial virus (RSV).

55. The chimeric PIV of claim 54, wherein the gene or genome segment encodes a RSV F and/or G glycoprotein or immunogenic domain(s) or epitope(s) thereof.

56. The chimeric PIV of claim 1 which is a complete virus.

57. The chimeric PIV of claim 1 which is a subviral particle. The chimeric PIV of claim 1 which is a virus.

58. A method for stimulating the immune system of an individual to induce protection against PIV which comprises administering to the individual an immunologically sufficient amount of the chimeric PIV of claim 1 combined with a physiologically acceptable carrier.

59. The method of claim 58, wherein the chimeric PIV is administered 2 in a dose of 103 to 107 PFU.

60. The method of claim 58, wherein the chimeric PIV is administered to the upper respiratory tract.

61. The method of claim 58, wherein the chimeric PIV is administered by spray, droplet or aerosol.

62. The method of claim 58, wherein the chimeric PIV and a second attenuated PIV are administered simultaneously as a mixture.

63. An immunogenic composition to elicit an immune response against PIV comprising an immunogenically sufficient amount of the chimeric PIV of claim 1 in a physiologically acceptable carrier to elicit PIV virus neutralizing antibodies.

64. The immunogenic composition of claim 63, formulated in a dose of 10^3 to 10^7 PFU.

65. The immunogenic composition of claim 63, formulated for administration to the upper respiratory tract by spray, droplet or aerosol.

66. The immunogenic composition of claim 63, wherein the chimeric PIV elicits an immune response against one or more virus(es) selected from HPIV 1, 3 HPIV2 and HPIV3.

67. The immunogenic composition of claim 66, wherein the chimeric PIV elicits an immune response against HPIV3 and another virus selected from HPIV 1, HPIV2 and HPIV3.